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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/54, 47/00

A1

(11) International Publication Number: **WO 99/39713**

(43) International Publication Date: 12 August 1999 (12.08.99)

(21) International Application Number: PCT/KR99/00064

(22) International Filing Date: 9 February 1999 (09.02.99)

(30) Priority Data:
1998/3671 9 February 1998 (09.02.98) KR

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**

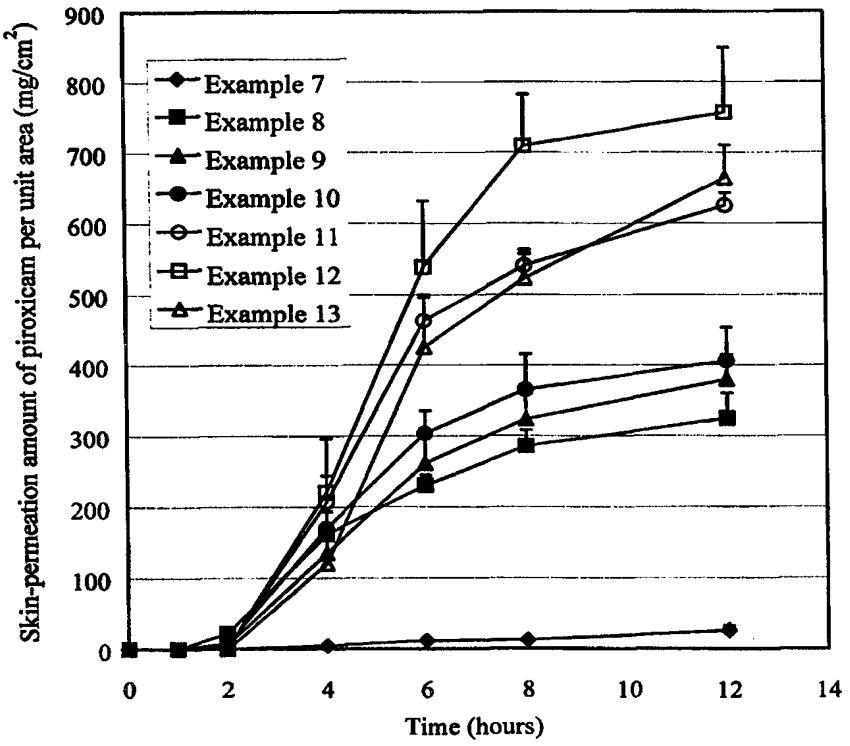
*With international search report.*

*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: PIROXICAM-CONTAINING HYDROALCOHOLIC GEL COMPOSITION

(57) Abstract

The present invention relates to a hydroalcoholic gel composition which not only can decrease the external loss of piroxicam but also can increase the permeation of piroxicam through skin remarkably, compared with conventional hydrogel preparation, by forming a film on the skin surface promptly without drug precipitation, using lower alkanol having from one to four carbon atoms as a main solvent. The composition according to the present invention comprises (a) 0.1~2 % by weight of piroxicam; (b) 40~60 % by weight of lower alkanol having from one to four carbon atoms; (c) 0.1~5 % by weight of hydroxypropylcellulose or hydrophobic derivatives of hydroxypropylmethylcellulose, optionally comprising hydroxypropylmethylcellulose or carbomer, as a polymer vehicle; (d) 0.1~20 % by weight of at least one absorption enhancer selected from the group consisting of diethyleneglycol monoethylether, polyoxyethyleneglycolated natural or hydrogenated castor oil, oleic acid and its alkali salt, and polysorbate; (e) 0.1~5 % by weight of at least one pH controlling agent selected from alkanolamines; and (f) water.



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# PIROXICAM-CONTAINING HYDROALCOHOLIC GEL COMPOSITION

## TECHNICAL FIELD

The present invention relates to a novel hydroalcoholic gel composition containing piroxicam as an active component; and more specifically, to a hydroalcoholic gel composition which not only can decrease the external loss of piroxicam but also can increase the permeation of piroxicam through skin remarkably, compared with conventional hydrogel preparation, by forming a film on the skin surface promptly without drug precipitation, using lower alkanol having from one to four carbon atoms as a main solvent.

## BACKGROUND ART

Piroxicam, which is a non-steroidal anti-inflammatory analgesic, shows potent anti-inflammatory activity and also analgesic activity. Therefore, it is used widely for treatment of rheumatoid arthritis and its related diseases, such as chronic rheumatism, deformable rheumatism, lumbago, ankylosing spondylitis, etc., and for analgesia and anti-inflammation related to stab and contusion.

Until now, piroxicam preparations have used oral administration as a main route of drug administration and have showed excellent activity. However, the following points are problems awaiting solution: their oral administration can induce systemic adverse effect and their long-term multiple dosing can induce gastrointestinal tract (GI tract) disturbance. To

decrease the above adverse effects, many external preparations for transdermal drug delivery have been studied and designed. The results of said researches show that topical application through skin can minimize adverse effects such as systemic adverse effect and GI tract disturbance and can express anti-inflammatory analgic effects.

However, piroxicam is slightly soluble in water, and has very low solubility in other solvent, i.e. oil and organic solvents. And it is generally known that piroxicam shows low skin permeability in case of transdermal application. Moreover, piroxicam hydrate that is formed by the expose to water shows lower solubility than piroxicam itself does, and forms gradually a precipitation that could not be absorbed through skin. It induces a problem, i.e. remarkable decrease of drug bioavailability. Therefore, at the point of drug characteristics, a design of hydroalcoholic gel using alkanol as a main solvent is an important method to solve the said problems.

As an example of prior arts, U.S. Patent 4,678,666 has disclosed piroxicam-containing external gel type preparation. The said external preparation is an aqueous hydrogel system containing piroxicam, which used carbomer, carboxymethylcellulose, hydroxyethylcellulose, or polyvinylpyrrolidone as a polymer vehicle, and water as a main solvent. However, since the hydrogel disclosed in the above prior art used less than about 40 w/w% of lower alkanol, especially ethanol, the hydrogel does not form gel but has sol characteristics in case of reducing the amount of water to less than 30 w/w%. Therefore, its application feeling becomes bad and skin permeability of piroxicam decreases remarkably.

Japan Patent Publication No. 63/313,731 and European Patent 453,603 have also disclosed piroxicam-containing external preparations,

liquid type and cream type of w/o emulsion, respectively. They used water and oil originated from fatty acids as a main solvent. Therefore, they are not related to the external preparation of hydroalcoholic gel type according to the present invention. Because the said external preparations according to the prior arts used water or oil as a main solvent, they need long time for drying and, therefore, could be loosed by being wiped with clothes and by washing from skin surface when they are applied to patient skin. Therefore, the said external preparations have a disadvantage that they show very low drug absorption, compared with dose.

Hydrogel preparation disclosed in U.S. Patent 5,436,241 is an hydroalcoholic gel that uses ethanol as a main solvent. A distinguishing mark is that the preparation uses tetrahydroxypropyl ethylenediamine, as a pH-controlling agent, instead of alkanolamines of prior art. (The said patent insisted that hydroalcoholic gel could not be prepared with alkanolamines due to loss of viscosity.) However, tetrahydroxypropyl ethylenediamine used in the said patent has a problem that caution against toxicity and adverse effects is needed for using as an excipient of medicine preparations, because the material is not listed in any medicine pharmacopeia, e.g., U.S., Europe, England and Korea pharmacopeia.

The present inventors have studied to solve the said disadvantages. As a result, we have developed the novel hydroalcoholic gel composition containing piroxicam, which has the following characteristics: the said composition can form a film at the applied part of skin without drug precipitation on the skin or without polymer aggregation by skin salt, and the said composition can show excellent drug absorption compared with piroxicam-containing external preparation according to prior arts.

Therefore, the object of the present invention is to produce novel hydroalcoholic gel composition containing piroxicam.

## DISCLOSURE OF INVENTION

The present invention relates to a piroxicam-containing hydroalcoholic gel composition that comprises (a) 0.1~2 % by weight of piroxicam; (b) 40~60 % by weight of lower alkanol having from one to four carbon atoms; (c) 0.1~5 % by weight of hydroxypropylcellulose or hydrophobic derivatives of hydroxypropylmethylcellulose, optionally comprising hydroxypropylmethylcellulose or carbomer, as a polymer vehicle; (d) 0.1~20 % by weight of at least one absorption enhancer selected from the group consisting of diethyleneglycol monoethylether, polyoxyethyleneglycolated natural or hydrogenated castor oil, oleic acid and its alkali salt, and polysorbate; (e) 0.1~5 % by weight of at least one pH controlling agent selected from alkanolamines; and (f) water.

The lower alkanols having from one to four carbon atoms, which is used as a main solvent in the present invention, may be ethanol, isopropanol, etc.. A preferred amount of the lower alkanol is 40~60 % by weight, more preferably 45~55 % by weight. Particularly, it is more preferable that the amount of the said lower alkanol is 1~3 times of that of water used (i.e., the amount of water is 1/3 ~ 1 times of that of lower alkanols used), and more preferably 1.2~2 times.

Because the composition according to the present invention uses lower alkanol having from one to four carbon atoms as a main solvent, it can form a film on skin surface without drug precipitation or polymer aggregation. Therefore, the composition makes external loss of piroxicam decreased, and also makes patient compliance improved.

The composition according to the present invention uses hydroxypropylcellulose (HPC) or hydrophobic derivatives of hydroxypropylmethylcellulose (HPMC), optionally comprising hydroxypropylmethylcellulose or carbomer, as a polymer vehicle. Their amount used is 0.1~5.0 % by weight, preferably 0.5~3.0 % by weight. Hydroxypropylmethylcellulose or carbomer acts as a improving agent for viscosity and application feeling. Carbomer may be carbomer 934 and carbomer 940. Hydrophobic derivatives of hydroxypropylmethylcellulose may be a product commercialized under the trade name "Sangelose" of Sankio Chem.

The said polymer materials are soluble in the mixture of lower alkanols and water, and can form a clear gel with water of less than 30 % by weight. Therefore, they are proper materials to form hydroalcoholic gel. On the other hand, conventional water-soluble polymers such as carboxymethylcellulose, hydroxyethylcellulose, etc. are not proper materials to be used in hydroalcoholic gel composition according to the present invention because they loose their viscosity or become cloudy at the condition that water content is less than 30 % by weight.

The preferred polymer combinations in the composition according to the present invention are showed in the following Table 1.

Table 1. Polymer combinations of hydroalcoholic gel

| Type | | Polymer combination | |
|---|---|---|---|
| Type 1 | Type 1-1 | HPC | - |
| | Type 1-2 | HPC | Carbomer |
| | Type 1-3 | HPC | HPMC |
| Type 2 | Type 2-1 | Sangelose | - |
| | Type 2-2 | Sangelose | Carbomer |
| | Type 2-3 | Sangelose | HPMC |

The composition according to the present invention comprises at least one absorption enhancer selected from the group consisting of diethyleneglycol monoethylether, polyoxyethyleneglycolated natural or hydrogenated castor oil, oleic acid and its alkali salt, and polysorbate. The amount of absorption enhancer is 0.1~20 % by weight, preferably 0.5~10 % by weight. In the said absorption enhancers, diethyleneglycol monoethylether may be a product commercialized under the trade name "Transcutol" of Gattefosse, polyoxyethyleneglycolated natural or hydrogenated castor oil may be a product commercialized under the trade name "Cremophor", and polysorbate may be a product commercialized under the trade name "Tween".

The said absorption enhancer not only directly increase skin permeability of piroxicam but also has excellent solubility for piroxicam (which is slightly soluble in lower alkanol and water) by its surface activation ability, thereby restraining precipitation of piroxicam on skin to indirectly contribute the total skin-permeation amount of piroxicam. That is, by using the said absorption enhancer along with the solvent of

40~60 % by weight of the said lower alkanol, it is possible to design piroxicam-containing gel composition for external use, from which skin permeation of piroxicam can be maximized. And the said absorption enhancer comprised in the composition according to the present invention has an advantage that it can form hydroalcoholic gel of pH 5.5~7.5 because it has an excellent dissolving power for piroxicam, which is insoluble in acidic or neutral condition.

The composition according to the present invention comprises 0.1~5 % by weight, preferably 0.5~2.0 % by weight, of at least one pH controlling agent selected from alkanolamines. The said alkanolamines may be triethanolamine, diisopropanolamine, etc. Ultimate pH of the composition according to the present invention is pH 5.5~7.5 preferably, but it is not restricted in the said range.

The composition according to the present invention can further comprise 0.1~20 % by weight, preferably 5~10 % by weight of alkylene glycol having from two to six carbon atoms as a humectant. And it can further comprise 0.1~5.0 % by weight, preferably 0.2~2.0 % by weight, of polypropyleneglycol urethane copolymer as an feeling-improving agent.

Polypropyleneglycol urethane copolymer (Polyolprepolymer-2, Penederm; its chemical name: poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-hydroxy-, polymer with 1,1′-methylene-bis-[4,isocyanatocyclohexane]) is a hydrophobic liquid polymer. Because it has a high affinity to stratum corneum, it can make skin irritation of external preparation decreased and can induce the wetting of stratum corneum even in case of using less than 2 % by weight. These are proper characteristics to improve application feeling of hydroalcoholic gel according to the present invention. The hydroalcoholic gel composition containing the said material can show

decreased skin irritation of alcohol, and furthermore can increase the amount of drug retained in skin because it resists against washing or wiping of external preparation from skin by water on the surface of skin or by clothes.

In addition, external gel composition according to the present invention may further comprise conventional amount of at least one selected from such flavors as menthol and camphor, and such preservatives as methyl parahydroxybenzoate and ethyl parahydroxybenzoate, as a conventional additive.

The external gel composition according to the present invention, which is a hydroalcoholic gel prepared by combinations of proper polymers and usage of lower alkanol having from one to four carbon atoms as a main solvent, can form a film on skin surface promptly without drug precipitation. Furthermore, by containing the said lower alkanol and absorption enhancer, the pharmaceutical composition makes external loss of piroxicam decreased, piroxicam bioavailability maximized and skin permeation remarkably increased, compared with piroxicam-containing topical gel according to prior art.

The hydroalcoholic gel composition according to the present invention may be prepared by the following methods:

At first, about 2/3 parts of total amount of lower alkanol ($C_1$-$C_4$) are mixed with water. Absorption enhancer and, if needed, humectant are added to the mixed solvent, and dissolved. To the resulting solution, alkanolamine is added as a pH-controlling agent. However, alkanolamine is not added in case of which carbomer is not contained as a polymer vehicle. In case of containing carbomer, carbomer is neutralized with

proper quantity of alkanolamine to the range of pH 5.5~6.0, and then carbomer be swelled and dissolved. Polymer vehicle is mixed with resultant solution, and swelled. At this point, in case of using carbomer, other polymers must be added and swelled only after swelling/dissolving and neutralization of carbomer are completed. Otherwise, the polymers, unstable at acidic or alkali condition, could be decomposed, and viscosity of gel preparation and skin permeation of drug could be decreased.

On the other hand, to residual parts of total amount of lower alkanol ($C_1$-$C_4$), piroxicam is added, and then residual quantity of alkanolamine is added thereby to obtain a clear solution of piroxicam. The resulting solution of piroxicam and other additives is added promptly to a vessel that contains the polymer swelled, and mixed thereby to prepare gel. If the said solution of piroxicam was stood for a long time, drug content might be decreased. Therefore, after drug is dissolved in solution, the resulting solution must be added promptly to the polymer mixture prepared to form a gel.

The external gel composition according to the present invention prepared by the said method, which is a transparent gel, produces cool feeling after application to skin, and is dried rapidly without stickiness thereby to form a thin film on the surface of skin. Particularly, the composition forms a film without coagulation that could be appeared by polymer precipitation due to salt of skin and without piroxicam precipitation (yellow deposit) due to forming piroxicam hydrate.

## BRIEF DESCRIPTION OF THE DRAWINGS

For a thorough understanding of the nature and objects of the invention, reference should be had to the following detailed description

taken in connection with the accompanying drawings in which:

Figure 1 shows the effects of lower alkanol (ethanol) content and absorption enhancer addition on the skin-permeation amount of piroxicam (◆-◆, Example 7; ■-■, Example 8; ▲-▲, Example 9; ●-●, Example 10; ○-○, Example 11; □-□, Example 12; △-△, Example 13).

Figure 2 shows the effect of absorption enhancer addition on the skin-permeation amount of piroxicam (◆-◆, Example 14; ■-■, Example 15; ▲-▲, Example 16; □-□, Example 17; ○-○, Example 18).

## MODES FOR CARRING OUT THE INVENTION

The present invention is described in more detail by Examples and Experiments as shown below but is not confined to the said scopes.

**Example 1.**

Table 2. Composition of Example 1.

| Components | Content (w/w%) |
|---|---|
| Piroxicam | 0.5 |
| Ethanol | 50 |
| Hydroxypropylcellulose | 3 |
| Diisopropanolamine | 0.2 |
| Diethyleneglycol monoethylether | 5 |
| Polyolprepolymer-2 | 0.5 |
| Propylene glycol | 10 |
| Benzyl alcohol | 2 |
| L-Menthol | 0.5 |
| Water | q.s. |
| Total | 100 |
| pH | 6.4 |

Diethyleneglycol monoethylether and propylene glycol were added to the mixed solvent of 35 g of ethanol and 25 g of water, and dissolved. To the resulting solution, hydroxypropylcellulose was added to swell.

On the other hand, piroxicam, diisopropanolamine and benzyl alcohol were added into residual parts of ethanol thereby to obtain piroxicam solution. The piroxicam solution prepared and other additives were added to the said mixture, in which polymer was present in swollen state, and then mixed. To the resultant mixture, water was added to prepare 100 g of hydroalcoholic gel.

**Example 2.**

Table 3. Composition of Example 2.

| Components | Content (w/w%) |
|---|---|
| Piroxicam | 0.5 |
| Ethanol | 50 |
| Hydroxypropylcellulose | 1.2 |
| Carbomer | 1 |
| Diisopropanolamine | 0.75 |
| Diethyleneglycol monoethylether | 5 |
| Polyolprepolymer-2 | 0.5 |
| Propylene glycol | 10 |
| Benzyl alcohol | 1 |
| L-Menthol | 2 |
| Water | q.s. |
| Total | 100 |
| pH | 6.2 |

Diethyleneglycol monoethylether and propylene glycol were added to the mixed solvent of 35 g of ethanol and 25 g of water, and dissolved. To the resulting solution, 0.6 g of diisopropanolamine was added to dissolve homogeneously, and then carbomer was added and swollen to become pH 5.5~6.0. And then, to the resulting solution, hydroxypropylcellulose was added and swollen.

On the other hand, piroxicam, diisopropanolamine (of residual quantity) and benzyl alcohol were added into residual parts of ethanol thereby to obtain piroxicam solution. The piroxicam solution prepared and

other additives were added to the said mixture, in which polymer was present in swollen state, and then mixed. To the resultant mixture, water was added to prepare 100 g of hydroalcoholic gel.

**Example 3.**

Table 4. Composition of Example 3.

| Components | Content (w/w%) |
|---|---|
| Piroxicam | 0.5 |
| Ethanol | 50 |
| Hydroxypropylcellulose | 2 |
| Hydroxypropylmethylcellulose | 0.7 |
| Diisopropanolamine | 0.2 |
| Diethyleneglycol monoethylether | 5 |
| Polyolprepolymer-2 | 0.5 |
| Propylene glycol | 10 |
| Benzyl alcohol | 2 |
| L-Menthol | 0.5 |
| Water | q.s. |
| Total | 100 |
| pH | 6.4 |

Diethyleneglycol monoethylether and propylene glycol were added to the mixed solvent of 35 g of ethanol and 25 g of water, and dissolved. To the resulting solution, hydroxypropylcellulose and hydroxypropylmethylcellulose were added and swollen.

On the other hand, piroxicam, diisopropanolamine and benzyl

alcohol were added into residual parts of ethanol thereby to obtain piroxicam solution. The piroxicam solution prepared and other additives were added to the said mixture, in which polymer was present in swollen state, and then mixed. To the resultant mixture, water was added to prepare 100 g of hydroalcoholic gel.

**Example 4~6.**

Table 5. Composition of Example 4~6.

| Components | Content (w/w%) | | |
|---|---|---|---|
| | Example 4 | Example 5 | Example 6 |
| Piroxicam | 0.5 | 0.5 | 0.5 |
| Ethanol | 50 | 50 | 50 |
| Sangelose | 3 | 1.5 | 2 |
| Carbomer | - | 1 | - |
| Hydroxypropylmethylcellulose | - | - | 1 |
| Diisopropanolamine | 0.2 | 0.75 | 0.2 |
| Oleic acid | 1 | 1 | 1 |
| Polyolprepolymer-2 | 0.5 | 0.5 | 0.5 |
| Propylene glycol | 10 | 10 | 10 |
| Benzyl alcohol | 2 | 1 | 2 |
| L-Menthol | 0.5 | 2 | 0.5 |
| Water | q.s. | q.s. | q.s. |
| Total | 100 | 100 | 100 |
| pH | 6.4 | 6.2 | 6.4 |

The hydroalcoholic gels of Example 4 to 6, which have

compositions of Table 5, were prepared in the same methods with Examples 1 to 3, respectively, except using hydrophobic hydroxypropylmethylcellulose derivative (Sangelose) instead of hydroxypropylcellulose and except using oleic acid instead of diethyleneglycol monoethylether.

**Example 7.**

Table 6. Composition of Example 7.

| Components | Content (w/w%) |
|---|---|
| Piroxicam | 0.5 |
| Ethanol | 30 |
| Hydroxypropylcellulose | 1 |
| Carbomer | 0.8 |
| Diisopropanolamine | 1 |
| Polyolprepolymer-2 | 0.5 |
| Propylene glycol | 10 |
| Benzyl alcohol | 1 |
| L-Menthol | 2 |
| Water | q.s. |
| Total | 100 |
| pH | 7.0 |

Propylene glycol were added to the mixed solvent of 20 g of ethanol and 40 g of water, and dissolved. To the resulting solution, 0.6 g of diisopropanolamine was added to dissolve homogeneously, and then carbomer was added and swollen to become pH 5.5~6.0. And then, to the

resulting solution, hydroxypropylcellulose was added to swell. The following process was performed according to the method of Example 2 to prepare a conventional hydrogel.

**Example 8~13.**

With various ethanol contents, piroxicam-containing hydroalcoholic gel compositions were prepared as follows:

Table 7. Composition of Example 8~13.

| Components | Content (w/w%) | | | | | |
|---|---|---|---|---|---|---|
| | Example 8 | Example 9 | Example 10 | Example 11 | Example 12 | Example 13 |
| Piroxicam | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Ethanol | 45 | 50 | 55 | 45 | 50 | 55 |
| Hydroxypropyl cellulose | 1 | 1 | 1 | 1 | 1 | 1 |
| Carbomer | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Diisopropanolamine | 1 | 1 | 1 | 1 | 1 | 1 |
| Diethyleneglycol monoethylether | - | - | - | 4.5 | 4.5 | 4.5 |
| Polyolprepolymer-2 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Propylene glycol | 10 | 10 | 10 | 10 | 10 | 10 |
| Benzyl alcohol | 1 | 1 | 1 | 1 | 1 | 1 |
| L-Menthol | 2 | 2 | 2 | 2 | 2 | 2 |
| Water | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| Total | 100 | 100 | 100 | 100 | 100 | 100 |
| pH | 7.0 | | | | | |

The hydroalcoholic gels of Example 8 to 13, which have compositions of Table 7, were prepared in the same methods with Examples 2, except the amount of components.

**Example 14~18.**

With various absorption enhancer contents, piroxicam-containing hydroalcoholic gel compositions were prepared as follows:

Table 8. Composition of Example 14~18.

| Components | Content (w/w%) | | | | |
|---|---|---|---|---|---|
| | Example 14 | Example 15 | Example 16 | Example 17 | Example 18 |
| Piroxicam | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Ethanol | 50 | 50 | 50 | 50 | 50 |
| Sangelose | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Carbomer | 1 | 1 | 1 | 1 | 1 |
| Diisopropanolamine | 1 | 1 | 1 | 1 | 1 |
| Diethyleneglycol monoethylether | - | 5 | - | - | - |
| Cremophor | - | - | 3 | - | 1 |
| Oleic acid | - | - | - | 1 | - |
| Tween 80 | - | - | - | - | 3 |
| Polyolprepolymer-2 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Propylene glycol | 10 | 10 | 10 | 10 | 10 |
| Benzyl alcohol | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| L-Menthol | 2 | 2 | 2 | 2 | 2 |
| Water | q.s. | q.s. | q.s. | q.s. | q.s. |
| Total | 100 | 100 | 100 | 100 | 100 |
| pH | 6.7 | | | | |

The hydroalcoholic gel of Example 14, which has the compositions of Table 8, was prepared in accordance with the same methods as in Examples 2, except using hydrophobic hydroxypropylmethylcellulose derivative (Sangelose) instead of hydroxypropylcellulose and except amount of diethyleneglycol monoethylether.

The hydroalcoholic gel of Example 15, which has the compositions of Table 8, was prepared in the same methods with Examples 2, except using hydrophobic hydroxypropylmethylcellulose derivative (Sangelose) instead of hydroxypropylcellulose.

The hydroalcoholic gel of Example 16, which has the compositions of Table 8, was prepared in the same methods with Examples 2, except using hydrophobic hydroxypropylmethylcellulose derivative (Sangelose) instead of hydroxypropylcellulose and except using polyoxyethyleneglycolated natural or hydrogenated castor oil (Cremophor) instead of diethyleneglycol monoethylether (Transcutol).

The hydroalcoholic gel of Example 17, which has the compositions of Table 8, was prepared in the same methods with Examples 2, except using hydrophobic hydroxypropylmethylcellulose derivative (Sangelose) instead of hydroxypropylcellulose and except using oleic acid instead of diethyleneglycol monoethylether (Transcutol).

The hydroalcoholic gel of Example 18, which has the compositions of Table 8, was prepared in the same methods with Examples 2, except using hydrophobic hydroxypropylmethylcellulose derivative (Sangelose) instead of hydroxypropylcellulose and except using polysorbate (Tween 80) instead of diethyleneglycol monoethylether (Transcutol).

**Experimental example 1.**

Hydrogels were prepared in the same methods with Examples 2, except the amount of polypropyleneglycol urethane copolymer. The skin irritation test of hydrogels prepared with various content of polypropyleneglycol urethane copolymer was performed, and the results are given in the following Table 9.

Table 9. Evaluation of skin irritation feeling

| Content (W/W %) of polypropyleneglycol urethane copolymer | Evaluation of skin irritation feeling*, ** |
|---|---|
| 0 | 2.5 |
| 0.5 | 1.8 |
| 1.0 | 1.4 |
| 2.0 | 0.9 |

* Standard of evaluation: 0 (no irritant), 1 (weekly irritant), 2 (normally irritant), and 3 (strongly irritant).

** Each data is a mean value that was evaluated by ten men.

**Experimental example 2. *In vitro* skin permeation test I using hairless mouse skin**

To investigate the skin permeation of piroxicam from conventional hydrogel (Example 7), hydroalcoholic gels (Example 8~10) in which no enhancer was contained, and hydroalcoholic gels (Example 11~13) in which diethyleneglycol monoethylether was contained as an enhancer, the skin-permeation test was performed using transdermal dissolution apparatus (Hanson Research) and Franz Cell (FDA Recommended) as follows. Each sample was withdrawn at scheduled time after dissolution

test was started, and fresh dissolution medium of the same amount as the sample withdrawn was refilled. The speed of stirrer was set at 500 rpm, and Franz Cell and media were maintained at 32°C. 10% PEG400 saline was prepared, and used as a media. Franz Cell used in the test has an inner volume of 7 ml, and an inner diameter of 15 mm. The plug of Franz Cell was set to be open toward the outside, so gel can be dried naturally and, at the same time, skin permeation can be progressed. Abdominal skin of hairless mouse was cut and used. 0.5 ml of each preparations of Examples according to the present invention were applied to the stratum corneum of skin set on Franz Cell, and then skin-permeation amounts of piroxicam from them were determined. The result was given in Figure 1.

As can be shown from Figure 1, skin-permeation amounts per unit area ($\mu g/cm^2$) for 12 hours after gel application were as follows:

Gels of Example 8~10, which contain 45~55 % by weight of ethanol, showed relatively high skin-permeation amount of 300~400 $\mu g/cm^2$ while conventional hydrogel of Example 7, which contains 30 % by weight of ethanol, showed very low skin-permeation amount of less than 50 $\mu g/cm^2$. However, hydroalcoholic gels of Example 11~13 according to the present invention, which contain absorption enhancer and 45~55 % by weight of ethanol, showed skin-permeation amount increased remarkably, of which values were 600~800 $\mu g/cm^2$.

**Experimental example 3. *In vitro* skin-permeation test II using hairless mouse skin**

To investigate skin-permeation amount of piroxicam from hydroalcoholic gel (Example 14) that does not contain absorption enhancer, hydroalcoholic gels of the present invention (Example 15~18) that contain

diethyleneglycol monoethylether, polyoxyethyleneglycolated natural and hydrogenated castor oil, oleic acid, and polysorbate, respectively, as an absorption enhancer, skin-permeation test was performed as the same method with Experimental Example 2. The result was given in Figure 2.

As can be shown from Figure 2, skin-permeation amounts per unit area ($\mu g/cm^2$) for 12 hours after gel application were as follows:

Hydroalcoholic gels of Example 15~18 according to the present invention, which contain absorption enhancer, showed skin-permeation amount increased remarkably, of which values were 500~850 $\mu g/cm^2$ while hydroalcoholic gel of Example 14, which does not contain absorption enhancer, showed skin-permeation amount of 300 $\mu g/cm^2$. Particularly, hydroalcoholic gels of Example 15~17 showed remarkably high skin-permeation amount of 700~850 $\mu g/cm^2$ . Therefore, it was proved that hydroalcoholic gel according to the present invention can provide optimum condition for skin permeation of piroxicam.

**Experimental example 4. *In vivo* anti-inflammation test using pedes edema induced by carrageenan**

To investigate inhibition effect of hydroalcoholic gel of the present invention against edema, the following experiment was performed:

Male Sprague-Dawley rats weighing about 200 g were used. A control group used six rats, and each test groups administered with gel preparation of the present invention used six rats. At first, 0.1 ml of 1 w/w % λ -carrageenan (Type IV) was administered to left pelma of all rats including control group injectively, and then pedes volumes were determined immediately after injection ($V_0$) and after 3.5 hours ($V_{3.5}$). Immediately after injection of λ -carrageenan, each test preparations of Example 12, 16,

and 17 according to the present invention were spread on dorsum of left foot of rat, and then dried naturally for about 2 min. Pedes volumes were determined with Plethysmometer (Ugo Basile Co.). Pedes swelling ratio (PSR) and edema inhibition ratio were calculated from each pedes volumes determined, using the following formula 1 and 2, and the result was given in Table 10.

[Formula 1]

$$\text{Pedes swelling ratio (PSR) (\%)} = \frac{V_{3.5} - V_0}{V_0} \times 100$$

[Formula 2]

$$\text{Edema inhibition ratio (\%)} = [1 - (\frac{\text{PSR of test group}}{\text{PSR of control group}})] \times 100$$

Table 10. Result of *in vivo* anti-inflammation test using pedes edema induced by carrageenan ($n \geq 6$).

| Groups | Pedes swelling ratio (PSR) (%) | Edema inhibition ratio (%) |
|---|---|---|
| Control | 67.72±18.14 | - |
| Administered with a gel of Example 12 | 18.97± 4.61* | 71.98± 6.08 |
| Administered with a gel of Example 16 | 26.41± 4.75* | 61.00± 7.02 |
| Administered with a gel of Example 17 | 23.74± 6.22* | 64.94± 9.18 |

* $p < 0.001$ by the t-test when compared to control.

Inhibition test against pedes edema induced by carrageenan, which is a *in vivo* anti-inflammation test model, is used frequently, and its significance is reported in arts. As can be shown from Table 10, groups administered with gels of Example 12, 16 and 17 of the present invention showed significant difference of pedes swelling ratio compared to control group, and edema inhibition ratios calculated with those PSR were 61~72 %. In inhibition test against pedes edema induced by carrageenan, more than about 60 % of PSR means that the test preparation has excellent anti-inflammatory effect. Because the said gel preparations showed high edema inhibition ratio of more than 60 %, it was conformed that hydroalcoholic gels of the present invention show excellent anti-inflammatory effect as well as skin-permeation amount increased remarkably.

**Experimental example 5. Stability test**

Hydroalcoholic gels of Example 13, 16 and 17 according to the present invention was packed and stored in 4℃, 20℃ and 40℃ for 6 months separately. Each samples was withdrawn after 6 months, and tested for appearance, weight deviation, microbial contamination and content. The test of piroxicam content was performed using high performance liquid chromatography (HPLC). The result was given in the following Table 11.

Table 11. Result of stability test (stored in 4℃, 20℃ and 40℃ for 6 months separately).

| Test items | Example 13 | | | Example 16 | | | Example 17 | | |
|---|---|---|---|---|---|---|---|---|---|
| | 4℃ | 20℃ | 40℃ | 4℃ | 20℃ | 40℃ | 4℃ | 20℃ | 40℃ |
| Appearance | no change | no change | no change | no change | no change | no change | no change | no change | no change |
| Weight deviation | no change | no change | no change | no change | no change | no change | no change | no change | no change |
| Microbial contamination | accep-tance | accep-tance | accep-tance | accep-tance | accep-tance | accep-tance | accep-tance | accep-tance | accep-tance |
| Content (%) | 100.3 | 100.1 | 99.4 | 101.2 | 100.6 | 98.9 | 99.7 | 100.8 | 99.2 |

As can be shown from Table 11, all gel preparations tested, according to the present invention, showed no change of appearance and weight deviation, and were acceptable for the standard of microbial contamination test. In the test results of content of piroxicam, all of them maintained more than 98 % of piroxicam content, without large change. Therefore, gel preparations according to the present invention have very excellent stability.

From the results of *in vitro, in vivo* and stability tests as mentioned above, it was certified that the piroxicam-containing hydroalcoholic gel composition of the present invention shows skin-permeation amount increased remarkably and strong anti-inflammatory effect as well as good stability, so it is an optimum piroxicam composition fitted in the purpose of the present invention.

In conclusion, the composition according to the present invention, which is a novel hydroalcoholic gel composition containing piroxicam as an active ingredient, can form a film without drug precipitation and polymer aggregation promptly after application on skin, and can provide the prevention of external loss of drug and the excellent application feeling. In addition, the absorption of piroxicam from the film was maximized, and the composition of the present invention showed skin-permeation amount increased remarkably compared to conventional piroxicam gel preparation. Strong anti-inflammatory effect was proved in animal experiment. Therefore, the composition according to the present invention provides a pharmaceutical composition, that is, an external preparation of piroxicam that can improve patient compliance, minimize external loss of drug, increase skin-permeation remarkably, and have strong anti-inflammatory effect.

# CLAIMS

1. A piroxicam-containing hydroalcoholic gel composition which comprises:
   (a) 0.1~2 % by weight of piroxicam;
   (b) 40~60 % by weight of lower alkanol having from one to four carbon atoms;
   (c) 0.1~5 % by weight of hydroxypropylcellulose or hydrophobic derivatives of hydroxypropylmethylcellulose, optionally comprising hydroxypropylmethylcellulose or carbomer, as a polymer vehicle;
   (d) 0.1~20 % by weight of at least one absorption enhancer selected from the group consisting of diethyleneglycol monoethylether, polyoxyethyleneglycolated natural or hydrogenated castor oil, oleic acid and its alkali salt, and polysorbate;
   (e) 0.1~5 % by weight of at least one pH controlling agent selected from alkanolamines; and
   (f) water.
2. The composition according to claim 1, wherein the said composition further comprises:
   (g) 0.1~20 % by weight of at least one humectant selected from alkylene glycol having from two to six carbon atoms; and/or
   (h) 0.1~5.0 % by weight of propylene glycol urethane copolymer.
3. The composition according to claim 1, wherein the amount of water is 1/3 ~ 1 times of that of lower alkanols.
4. The composition according to any one of claims 1 to 3, wherein the said polymer is hydroxypropylcellulose, optionally comprising hydroxypropylmethylcellulose or carbomer.

5. The composition according to any one of claims 1 to 3, wherein the said polymer is hydrophobic derivatives of hydroxypropylmethylcellulose, optionally comprising hydroxypropylmethylcellulose or carbomer.

6. The composition according to any one of claims 1 to 3, wherein the said composition has pH 5.5~7.5.

7. The composition according to any one of claims 1 to 3, wherein the said composition further comprises at least one species of pharmaceutically acceptable additives selected from the group consisting of conventional preservatives and flavors.

FIG. 1

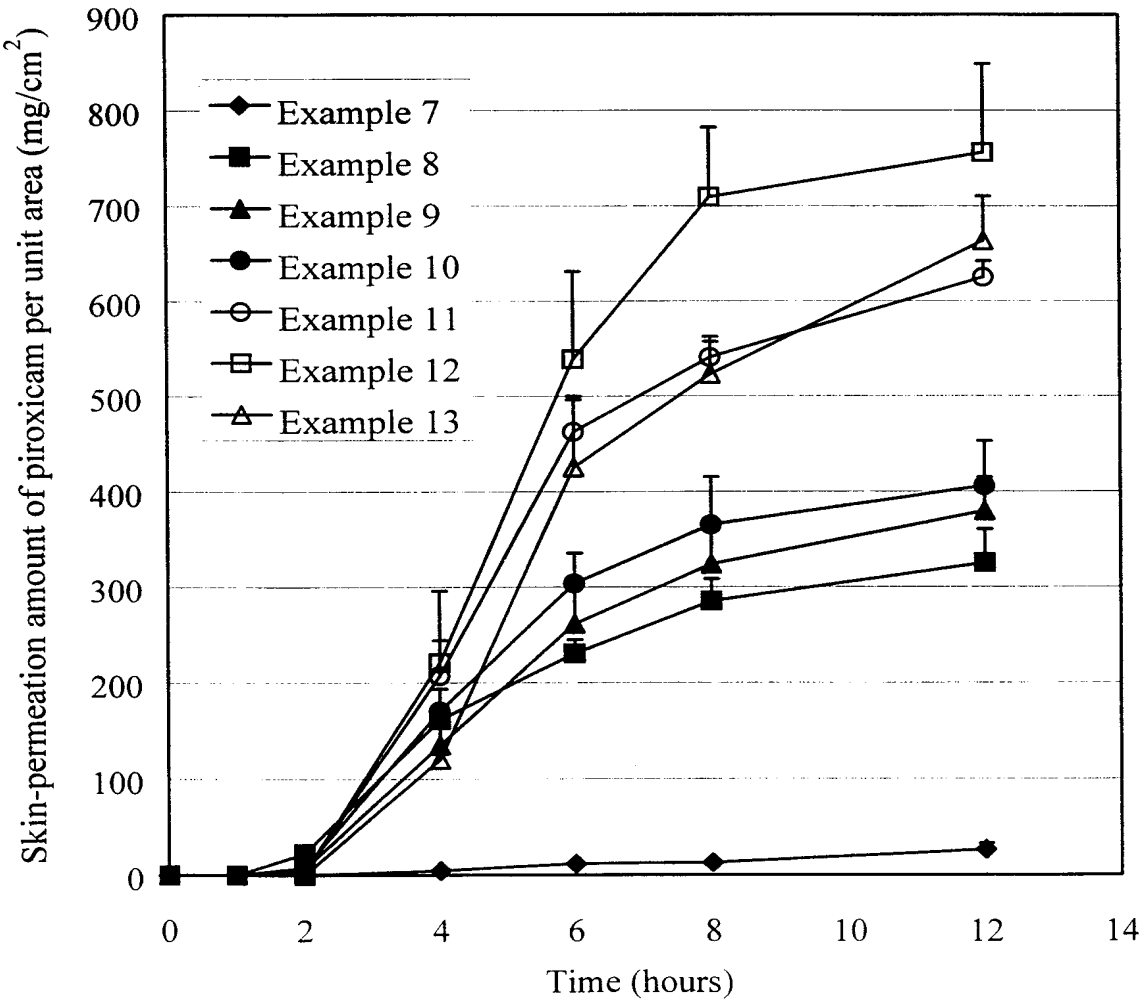
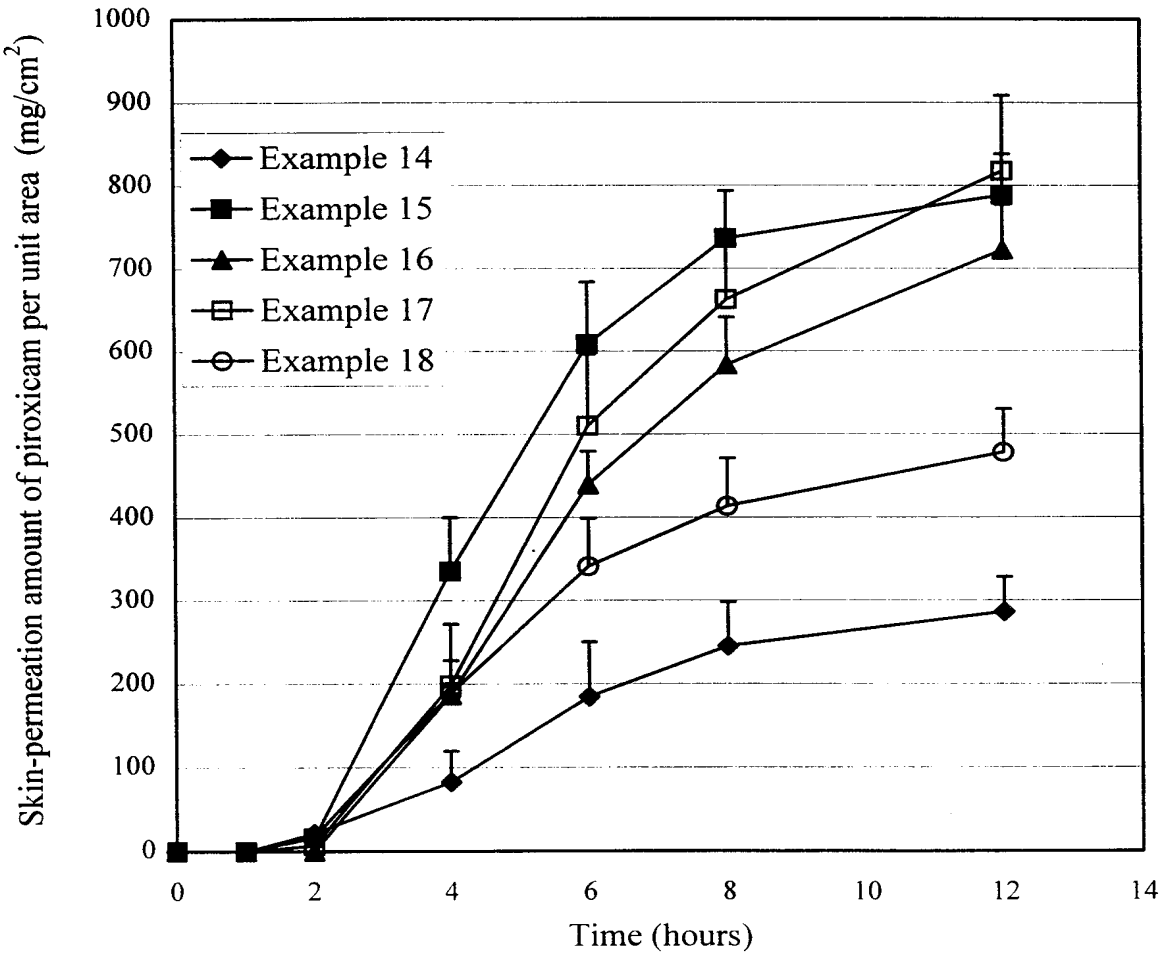

Skin-permeation amount of piroxicam per unit area (mg/cm2)
900
800
700
600
500
400
300
200
100
0
0
2
4
6
8
10
12
14
Time (hours)
Example 7
Example 8
Example 9
Example 10
Example 11
Example 12
Example 13

FIG. 2


Skin-permeation amount of piroxicam per unit area (mg/cm2)
1000
900
800
700
600
500
400
300
200
100
0
Example 14
Example 15
Example 16
Example 17
Example 18
0
2
4
6
8
10
12
14
Time (hours)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00064

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: A 61 K 31/54, 47/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: A 61 K 31/54, 47/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CAS

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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„&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 07 May 1999 (07.05.99) | 04 June 1999 (02.06.99) |

| Name and mailing adress of the ISA/AT | Authorized officer |
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| Austrian Patent Office<br>Kohlmarkt 8-10; A-1014 Vienna<br>Facsimile No. 1/53424/535 | Mosser<br>Telephone No. 1/53424/435 |

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